

Economic Evaluation of Controlled-release Oxycodone vs Oxycodone-Acetaminophen for Osteoarthritis Pain of the Hip or Knee

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Objective: To examine, in routine practice, the effectiveness and cost-effectiveness of oxycodone (OxyContin®) compared with standard therapy for osteoarthritis pain.

Study Design: Open-label active-controlled randomized naturalistic 4-month study of oxycodone vs a combination of oxycodone-acetaminophen (Percocet®).

Methods: Outcomes and health resource utilization data were collected by telephone interview. Effectiveness was measured among 485 patients as the proportion having at least 20% improvement from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index pain score. Quality-adjusted life-years (QALYs) were calculated from the Health Utilities Index 3 score. Cost-effectiveness was measured as cost per patient improved and the QALYs gained, using generic oxycodone-acetaminophen in the base case for the healthcare and societal perspectives. Uncertainty was evaluated using multiple 1-way sensitivity analyses and cost-effectiveness acceptability curves.

Results: Improvement occurred in 62.2% of patients with oxycodone and in 45.9% of patients with oxycodone-acetaminophen ($P < .001$). After adjustment for baseline differences, 0.0105 QALYs were gained with oxycodone compared with oxycodone-acetaminophen ($P = .17$). The mean societal costs per patient during 4 months were \$7379 and \$7528 for oxycodone and oxycodone-acetaminophen, respectively ($P = .33$). Oxycodone was more effective and less costly than oxycodone-acetaminophen based on the societal perspective (including costs associated with time lost). Based on the healthcare perspective (excluding costs associated with time lost), the cost-effectiveness of oxycodone was \$4883 per patient improved and \$75 810 per QALY gained. The base-case results were robust.

Conclusions: From the societal perspective, oxycodone was more effective and less costly than oxycodone-acetaminophen. From the healthcare perspective, oxycodone (compared with generic oxycodone-acetaminophen) fell within the acceptable range of cost-effectiveness between \$50 000 and \$100 000 per QALY gained.

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Most patients seek medical treatment because of the symptomatic chronic pain associated with moderate-to-severe OA. The main goal of OA therapy is to control chronic pain. The American College of Rheumatology recommends a progressive approach to oral analgesic therapy in patients with OA based on pain intensity, disease stage, and risk of medication toxicity. Prescription nonsteroidal anti-inflammatory drugs (NSAIDs), including coxibs, are recommended for moderate-to-severe OA. However, there is evidence that chronic use of NSAIDs may be associated with significant gastrointestinal and renal toxicity and with serious cardiac events.⁵⁻⁹ In 2004, rofecoxib (Vioxx®) was withdrawn from the market because of an increased incidence of myocardial infarction and stroke associated with its use.¹⁰ In patients for whom NSAIDs are ineffective or who are at high risk of chronic pain, the American College of Rheumatology¹¹ and the American Geriatrics Society¹² recommend stronger analgesic treatment with opioids. OxyContin® is a controlled-release brand of oxycodone that has been shown to decrease moderate-to-severe pain in patients with malignant and chronic nonmalignant conditions, including OA.^{13,14} (Unpublished data, February 11, 2000, Marcie E. Strauss, MPH).

The efficacy of oxycodone has been shown in controlled clinical trials. However, health system decision makers increasingly require evidence of effectiveness in routine practice settings and of cost-effectiveness. No previous studies were identified that examined the cost-effectiveness of oxycodone. Given that oxycodone is an approved and widely used treatment, this study was designed to compare oxycodone treatment with the

Osteoarthritis (OA) affects approximately 21 million people in the United States and is associated with a significant burden in terms of morbidity and costs.¹ Persons with moderate-to-severe OA may experience significant disability, reduced productivity, and an overall decrease in quality of life (QOL).²⁻⁴

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standard treatment of a combination of oxycodone-acetaminophen (Percocet®) in a routine practice setting that included health resource utilization in the treatment of OA pain. To respond to the interests of diverse audiences, including clinicians and third-party payers, we examined the cost-effectiveness results from the societal and healthcare system (HCS) perspectives.

METHODS

Study Design and Patient Population

This study was a multicenter open-label randomized naturalistic 4-month parallel-group design of the analgesic effectiveness of oxycodone every 12 hours vs oxycodone-acetaminophen as needed. Patients with moderate-to-severe pain from OA of the hip or knee received a platform of usual care. Patients were recruited from 50 sites across all census regions of the United States. The study included patients ≥ 40 years of age with OA of the hip or knee for at least 3 months who experienced moderate-to-severe OA pain that was not adequately controlled with short-acting opioid therapy. Osteoarthritis history in the most affected joint had to be documented by referral from the patient's primary care physician or by medical history and physical examination completed by one of us (CC), including radiologic evidence of OA within the past 2 years. Four to 7 days before randomization, patients had to have taken 2 or more tablets of a short-acting opioid per day (equivalent daily dose of ≥ 10 mg of oxycodone) for moderate-to-severe OA pain. Data were collected at the physician's office at baseline and at study termination (month 4).

Usual care generally included prescription medications (except for long-acting opioids), over-the-counter analgesics, herbal supplements or medications, nonpharmacologic interventions (eg, massage and biofeedback), non-protocol-mandated physician visits, and hospitalizations. Alterations in usual care could be made during the course of treatment, but no long-acting opioids other than the study medication could be prescribed except for indications other than OA pain (eg, dental procedures) for a period of less than 7 consecutive days, with only 1 such period during the study. Subjects had to remain on study medication as their primary opioid agent for OA pain. All subjects continued to have access to NSAID therapy, and subjects in the oxycodone group received immediate-release 5-mg capsules of oxycodone every 4 to 6 hours as needed (≤ 15 mg/d), as prescribed by one of us (CC) as rescue medication. Subjects in the oxycodone-acetaminophen group who were receiving a total daily dose of 4 g of acetaminophen (ie, 12 tablets of oxycodone-acetaminophen per day, or fewer if using anal-

gesics containing acetaminophen) were eligible to receive immediate-release 5-mg capsules of oxycodone as rescue medication at the discretion of the prescriber.

Outcomes Measures

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert 3.0 and the Health Utilities Index 3 (HUI3) health-related QOL (HRQOL) instruments were administered at baseline and at months 1, 2, 3, and 4 by telephone interview using a Web-based case report form. The WOMAC Likert 3.0 is a self-administered disease-specific HRQOL instrument with a total score and 3 subscale scores (pain, stiffness, and physical functioning).¹⁵ For the cost-effectiveness analysis (CEA), effectiveness was measured as the proportion of "patients improved," defined per the American College of Rheumatology¹⁶ guidelines as a 20% improvement in the WOMAC pain score in the study hip or knee from baseline to month 4.

Most OA trials measure HRQOL using the WOMAC scale (an OA-specific HRQOL instrument). However, the WOMAC scale does not provide a unidimensional generic preference-based measure of HRQOL that can be used in cost-utility analyses (CUAs). Consequently, the HUI3, which is such a generic instrument, was included in this study.

The HUI3 was used to measure the following 8 attributes of HRQOL: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain/discomfort.¹⁷ The instrument provides an overall utility score (range, -0.36 to 1.00), with 0.00 indicating death and 1.00 indicating perfect health. The overall HUI3 utility score is used for calculating quality-adjusted life-years (QALYs) for the CUA.

Health Resource Utilization and Costing

Health resource utilization data (related to OA pain only) were collected by telephone interview using a Web-based case report form at weekly intervals, including medications, healthcare providers, hospitalizations and emergency department visits, diagnostic tests and procedures, home healthcare services, assistive devices, and time lost from paid work activities and from unpaid regular activities for the patient, family, and friends.

All resource utilization was costed using US prices and reimbursement rules. The market price of oxycodone in the United States in 2003 was \$1.3439 per 10-mg tablet.¹⁸ Medications were costed using the 2003 *Drug Topics Red Book*¹⁸ mean wholesale price. The generic cost of oxycodone-acetaminophen was used in the base-case analysis. Medical devices, equipment, prosthetics, and orthotics were costed using durable medical equipment fee schedules.¹⁹ The costs of all physician and

clinic visits, healthcare professional consultations, and telephone contacts were estimated based on the unadjusted payment schedule for the service rendered as set forth in the Medicare Resource-Based Relative-Value Scale.²⁰ Costs of procedures and diagnostic tests were estimated using the global Medicare fee payment for non-facilities as set forth in the Medicare Resource-Based Relative-Value Scale.²⁰ Hospital emergency department or urgent care center visits were costed using estimates by Williams.²¹ Home healthcare services were costed using estimates from the home health prospective payment system rates paid by Medicare.²²⁻²⁴ Costs of time lost from activities were valued using the mean hourly earnings in 2001 from the labor force, employment, and earnings from the Statistical Abstracts of the United States.²⁵ Time lost from work and time lost from normal activities and from unpaid regular activities for family and friends were valued equally for all aspects of time lost. All costs were adjusted to 2005 US dollars using the Consumer Price Index for medical care.²⁶

Perspectives

Analyses were undertaken from the HCS and societal perspectives. The HCS perspective included costs for medications (prescription, over-the-counter, and herbal medications), healthcare visits (physician, nurse, and specialist visits), hospitalizations and emergency department visits, diagnostic tests and procedures, home healthcare services, and assistive devices. The societal perspective also included time lost from paid work and unpaid regular activities for the patient and family and friends.

Cost-effectiveness Analysis

The CEA compared the costs and outcomes of treatment with oxycodone with those of treatment with oxycodone-acetaminophen, estimated as the cost per patient improved. The CUA estimated the cost per QALY gained, derived from the area under the curve analysis of the HUI3 scores during 4 months, after adjustment for baseline differences.

Sensitivity Analysis

Sensitivity analyses were performed to test the robustness of the results. Uncertainty in the cost-effectiveness and cost-utility estimates was captured through 1-way sensitivity analyses and probabilistic sensitivity analyses. The following variables were varied in the 1-way sensitivity analyses: (1) the mean incremental efficacy measure per patient (proportion of patients improved) was varied using the upper and lower 90% confidence intervals for the difference in effectiveness between groups, (2) the mean 4-month incremental cost

per patient was varied using the upper and lower 90% confidence intervals for the 4-month difference in cost between groups, (3) the branded cost of Percocet was used (the base case was the generic cost), (4) the office visits and telephone contacts were assumed to be 50% nurse initiated and 50% physician initiated (the base case was 100% physician initiated), and (5) the health resource utilization associated with adverse effects of OA treatment (ie, study medication only) was added to the total OA-related cost during 4 months. Probabilistic results were generated by bootstrapping the trial results 1000 times, and the results were reported as cost-effectiveness acceptability curves.²⁷⁻²⁹

Statistical Analysis

Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC). Statistical tests were 2-sided, with a significance level of $P < .05$. Missing data were imputed using last observation carried forward for the WOMAC scale (20% in the oxycodone group and 18% in the oxycodone-acetaminophen group) and for the HUI3 instrument (34% in the oxycodone group and 23% in the oxycodone-acetaminophen group), provided that a post-baseline measurement was available.

Hot-deck imputation³⁰⁻³² was used for missing cost data (16% in the oxycodone group and 8% in the oxycodone-acetaminophen group). Patients with missing data were matched to a group of "similar" patients with complete data on the following variables: treatment group, age (± 10 years), sex, and severity of current OA pain (moderate vs severe). Logistic regression analysis was used to test the difference in the proportion of patients with a 20% improvement in pain since baseline.

RESULTS

Patient Demographics and Baseline Health Resource Utilization

A total of 526 patients comprised the safety population; 267 randomized to the oxycodone group and 259 to the oxycodone-acetaminophen group. Sixty-nine patients in the oxycodone group and 46 patients in the oxycodone-acetaminophen group dropped out or discontinued the study early. One death from lung cancer was reported in the oxycodone-acetaminophen group. Sixty-four percent of the patients in the oxycodone group reported at least 1 adverse event, compared with 46% in the oxycodone-acetaminophen group.

Five hundred thirteen patients were included in the intent-to-treat analysis (all subjects who were randomized and had taken at least 1 dose of study medication and had at least 1 post-baseline measurement); 261

Table 1. Health Resource Utilization During 4 Months

Resource Utilization	Oxycodone-Acetaminophen Group (n = 252)	Oxycodone Group (n = 261)
Discrete variables, No. of resources utilized [No. of patients]		
Osteoarthritis-related emergency department visits	10 [9]	9 [7]
Osteoarthritis-related hospitalizations	0 [0]	0 [0]
Physician or nurse visits	284 [110]	287 [122]
Healthcare practitioner telephone contacts	502 [135]	815 [179]
Other healthcare professional visits	382 [59]	327 [53]
Diagnostic tests and procedures	413 [88]	324 [89]
Orthopedic devices and equipment used or purchased	381 [152]	329 [144]
Continuous variables, mean \pm SD		
Home healthcare nurse for medical care, h	8 \pm 2	53 \pm 2
Home healthcare aide for medical care, h	70 \pm 3	109 \pm 5
Home healthcare aide for nonmedical care, h	1745 \pm 16	1820 \pm 30
Lost paid employment for family or friends, h	3.3 \pm 19.7	1.7 \pm 9.8
Lost paid employment for patient, h	7.5 \pm 34.5	6.2 \pm 31.8
Cutback on normal activities, d	33.4 \pm 32.4	26.8 \pm 28.3
Family or friends assisted patient, h	71.9 \pm 141.7	59.2 \pm 131.5

Resource use was not imputed or adjusted for the duration of time in study and was reported for all observed data regardless of patient completion status.

patients received oxycodone and 252 received oxycodone-acetaminophen. The groups were reasonably well balanced in terms of demographics and health resource utilization, with some differences noted in telephone contacts, hospitalizations and emergency department visits, assistive devices, and hours spent by families or friends assisting the patient (an appendix containing the demographic and health resource utilization variables at baseline is available from the author).

Health Resource Utilization and Costs During 4 Months

Compared with the oxycodone-acetaminophen group, more patients in the oxycodone group had healthcare practitioner telephone contacts and used more service hours of a home health aide or nurse. Patients in the oxycodone-acetaminophen group lost more hours from employment and from normal activities than patients in the oxycodone group. Time lost was the largest cost driver in the analysis from the societal perspective (Table 1).

The total OA-related HCS costs per patient for months 1 to 4 were greater for patients in the oxycodone group compared with patients in the oxycodone-acetaminophen group (\$1951 vs \$1155), driven by prescription medication costs (\$751 vs \$134) and home healthcare service costs (\$595 vs \$467) (Table 2). The total OA-related societal costs per patient for months 1 to 4 were lower for patients in the oxycodone group compared with patients in the oxycodone-acet-

aminophen group (\$7379 vs \$7528, $P = .33$), driven by costs associated with time lost from activities in the oxycodone-acetaminophen group.

Effectiveness

The oxycodone group had a larger proportion of patients who improved compared with patients in the oxycodone-acetaminophen group (62.2% vs 45.9%, $P < .001$). Patients in the oxycodone group also gained 0.0105 QALYs during the 4-month study compared with patients in the oxycodone-acetaminophen group ($P = .17$) (Table 3).

Base-case Incremental Cost-effectiveness Analysis

From the HCS perspective, the incremental mean cost per patient was \$796, and the difference in the proportion of patients improved was 0.163. Therefore, oxycodone was more costly and more effective than oxycodone-acetaminophen, with an incremental cost-effectiveness ratio of \$4883 per patient improved (Table 3).

From the societal perspective, the incremental mean cost per patient was \$149 less in the oxycodone group compared with the oxycodone-acetaminophen group. Therefore, oxycodone was less costly and more effective than oxycodone-acetaminophen (ie, treatment with oxycodone dominated treatment with oxycodone-acetaminophen) (Table 3).

Base-case Incremental Cost-utility Analysis

From the HCS perspective, the incremental mean

Table 2. Osteoarthritis-related Costs During 4 Months*

Cost, \$	Oxycodone-Acetaminophen (Percocet®) Group (n = 244)	Oxycodone Group (n = 241)	Difference (Oxycodone Group Minus Oxycodone-Acetaminophen Group)
Per patient			
Medications			
Prescription	134 ± 61	751 ± 420	617
Over-the-counter, herbals, constipation, mood, sleep	83 ± 110	84 ± 120	1
Physician or nurse visits	295 ± 429	371 ± 524	76
Diagnostic tests and procedures	93 ± 273	69 ± 186	-24
Osteoarthritis-related hospitalizations	0 ± 0	0 ± 0	0
Osteoarthritis-related emergency department visits	16 ± 85	11 ± 74	-5
Home healthcare services	467 ± 3405	595 ± 3235	128
Orthopedic devices and equipment from healthcare system perspective	67 ± 111	70 ± 127	3
Orthopedic devices and equipment from societal perspective	84 ± 139	86 ± 160	2
Lost time			
Paid employment for patient	157 ± 711	146 ± 705	-11
Paid employment for family or friends	72 ± 406	50 ± 249	-22
Unpaid regular activities for family or friends	1577 ± 3094	1376 ± 2814	-201
Cutback days on normal activities for patient	4550 ± 4124	3840 ± 3681	-710
Total			
From healthcare perspective	1155 ± 3434	1951 ± 3465	796
From societal perspective	7528 ± 7421	7379 ± 6741	-149

*Data are given as mean ± SD unless otherwise indicated. Costs for patients in the study for a duration less than 4 weeks were imputed using the hot-deck method of imputation.

The population used for analysis was reduced to a total of n = 485 (n = 241 for oxycodone and n = 244 for oxycodone-acetaminophen). Patients were excluded for whom no follow-up measure of the Western Ontario and McMaster Universities Index (WOMAC) pain score was available, since it was not possible to calculate the changes in WOMAC pain score.

cost per patient was \$796, and 0.0105 QALYs were gained in the oxycodone group compared with the oxycodone-acetaminophen group. Therefore, oxycodone was more costly and more effective than oxycodone-acetaminophen, with an incremental cost-utility ratio of \$75 810 per QALY gained (Table 3).

From the societal perspective, the incremental mean cost per patient was \$149 less in the oxycodone group compared with the oxycodone-acetaminophen group. Because oxycodone was less costly and more effective than oxycodone-acetaminophen, an incremental cost-utility ratio was not calculated. Treatment with oxycodone dominated treatment with oxycodone-acetaminophen (Table 3).

Sensitivity Analysis

Cost-effectiveness Analysis. In the 1-way sensitivity analyses from the HCS perspective, the CEA results ranged from a single dominant result to \$8884 per

patient improved (Table 4). The 1 dominant result occurred when the brand cost of oxycodone-acetaminophen was used instead of the generic cost. The probability that oxycodone is cost-effective is 52% at a ceiling ratio of \$5000 per patient improved. The curve plateaus near 100% at a threshold of \$10 000 per patient improved (figure not shown).

In the 1-way sensitivity analyses from the societal perspective, 6 of 7 results fell in win-win quadrants (Table 4). The probability that oxycodone is cost-effective is 91% at a ceiling ratio of \$5000 per patient improved (figure not shown).

Cost-utility Analysis. In the 1-way sensitivity analyses from the HCS perspective, the cost-utility results varied from oxycodone being dominated (lose-lose quadrant) to oxycodone dominating (win-win quadrant) (Table 4). Five of 7 results, however, fell in the upper right quadrant of the cost-effectiveness plane, with incremental cost-utility ratios ranging from \$26 762 to

Table 3. Base-case Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group

Analysis	HCS Perspective	Societal Perspective
Total cost, \$		
Oxycodone group	1951	7379
Oxycodone-acetaminophen group	1155	7528
Difference	796	-149
Proportion of patients improved		
Oxycodone group	0.622	0.622
Oxycodone-acetaminophen group	0.459	0.459
Difference	0.163	0.163
Cost per patient improved, \$*	4883	Win-win
Quality-adjusted life-years (QALYs) gained		
Oxycodone group	0.1551	0.1551
Oxycodone-acetaminophen group	0.1492	0.1492
Unadjusted difference between QALYs gained	0.0059	0.0059
Difference between treatment groups in resource utilization at baseline (oxycodone group minus oxycodone-acetaminophen group)	-0.014	-0.014
Effect of this resource utilization difference on QALYs gained	-0.0046	-0.0046
Adjusted difference between QALYs gained†	0.0105	0.0105
Cost per QALY gained, \$‡	75 810	Win-win

*The cost per patient improved is the incremental mean cost per patient (oxycodone group minus oxycodone-acetaminophen group) divided by the difference in the proportion of patients improved (oxycodone group minus oxycodone-acetaminophen group).

†The QALYs gained are adjusted for baseline differences.

‡The cost per QALY gained is the incremental mean cost per patient (oxycodone group minus oxycodone-acetaminophen group) divided by the incremental QALYs gained (oxycodone group minus oxycodone-acetaminophen group).

\$125 048 per QALY gained. The dominated result occurred when the incremental cost-effectiveness was set at its lower 90% confidence limit. The dominating result occurred when the brand cost of oxycodone-acetaminophen was used. The probability that oxycodone was cost-effective was 29% at the decision threshold of \$50 000 per QALY gained and 60% at \$100 000 per QALY gained (Figure 1).

From the societal perspective, the cost-utility results also varied from oxycodone being dominated (lose-lose quadrant) to oxycodone dominating (win-win quadrant) (Table 4). Five of 7 results indicated that oxycodone dominated (win-win quadrant). As from the HCS perspective, the dominated result occurred when the incremental effectiveness was set at its lower 90% confidence limit. The probability that oxycodone was cost-effective was 77% at the decision threshold of \$50 000 per QALY gained and 84% at \$100 000 per QALY gained (Figure 2).

DISCUSSION

Patients in the oxycodone group fared better than the patients in the oxycodone-acetaminophen group, as

measured by the incremental proportion of patients improved (0.163, $P < .001$) and by the number of QALYs gained (0.0105 QALYs) during 4 months. Therefore, the findings in terms of efficacy were robust as measured by the improvement on the WOMAC pain scale.¹⁶ The mean gain of 0.0105 QALYs during 4 months was not statistically significant but is equivalent to a gain of 0.0315 QALYs during 1 year and is equivalent to a mortality rate reduction of 0.0315.

In terms of costs, the findings differ depending on the perspective of the analysis. From the HCS perspective, oxycodone was more costly than oxycodone-acetaminophen by \$796 per patient, largely driven by the higher cost of prescription medications in the oxycodone group. From the societal perspective, when the cost of time lost from work and regular activities for the patient, family, and friends was included, oxycodone was less costly than oxycodone-acetaminophen.

Cost-effectiveness Analysis

It is difficult to assess whether the cost of \$4883 per patient improved during 4 months is a good value. This decision requires comparison with other CEA results reported using the same metric of patients improved. A

Table 4. Cost-effectiveness and Cost-utility Analyses From the Healthcare System (HCS) and Societal Perspectives Among 241 Patients in the Oxycodone Group and 244 Patients in the Oxycodone-Acetaminophen Group: One-way Sensitivity Analysis*

Analysis	Mean Cost Difference, \$		Difference in Proportion of Patients Improved	Mean Cost per Patient Improved, \$		QALYs Gained	Mean Cost per QALY Gained, \$	
	HCS Perspective	Societal Perspective		HCS Perspective	Societal Perspective		HCS Perspective	Societal Perspective
Base case	796	-149	0.163	4883	Win-win	0.0105	75 810	Win-win
Upper 90% CI for cost-effectiveness	796	-149	0.2364	3367	Win-win	0.0230	34 609	Win-win
Lower 90% CI for cost-effectiveness	796	-149	0.0896	8884	Win-win	-0.0020	Lose-lose	74 500†
Total cost for upper 90% CI for cost-effectiveness	1313	912	0.163	8055	5595	0.0105	125 048	86 857
Total cost for lower 90% CI for cost-effectiveness	281	-1210	0.163	1724	Win-win	0.0105	26 762	Win-win
Total cost using brand oxycodone-acetaminophen	-122	-1068	0.163	Win-win	Win-win	0.0105	Win-win	Win-win
Total cost using 50% physician visits and 50% nurse visits	763	-183	0.163	4681	Win-win	0.0105	72 667	Win-win
Total cost including health resource utilization associated with adverse effects of osteoarthritis treatment	803	-143	0.163	4926	Win-win	0.0105	76 476	Win-win

*Win-win indicates oxycodone is more effective and less costly than oxycodone-acetaminophen; and lose-lose, oxycodone is less effective and more costly than oxycodone-acetaminophen.

†This cost-utility estimate is for oxycodone-acetaminophen compared with oxycodone.

QALYs indicates quality-adjusted life-years; CI, confidence interval.

suitable comparison is a multicenter 1-year prospective randomized trial that compared "appropriate care plus viscosupplementation with hylan G-F 20" with "appropriate care without hylan G-F 20" for treatment of patients with OA of the knee.³³ The cost-effectiveness ratio of approximately \$2703 per patient improved during 1 year with hylan G-F 20 was less than the cost-effectiveness ratio in the present study.

The cost-effectiveness acceptability curve is a graphical method of summarizing uncertainty in cost-effectiveness estimates that considers costs and effects simultaneously.^{27-29,34-37} The cost-effectiveness acceptability curves in our study illustrated that the probability that oxycodone was cost-effective was 52% at \$5000 per patient improved from the HCS perspective. Decision

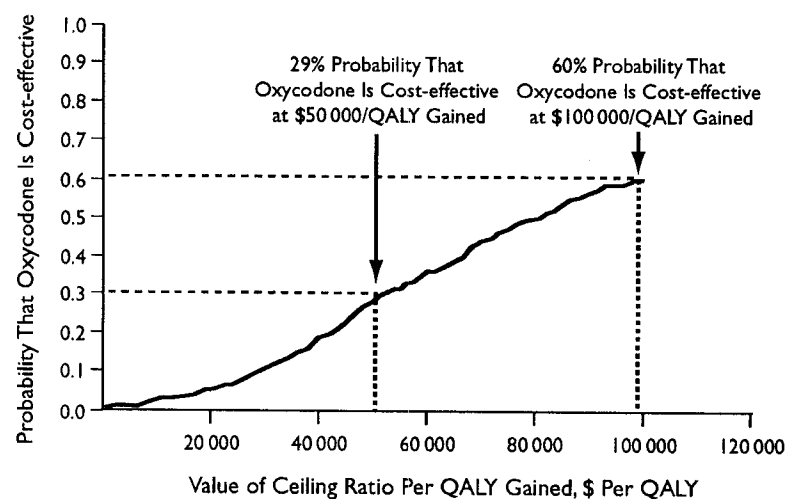
makers responsible for allocating healthcare resources will have to weigh this option against other choices.

Considering the CEA results from the societal perspective, the results are clearly in favor of oxycodone. Compared with oxycodone-acetaminophen, oxycodone increases the proportion of patients improved and was less costly. The probability that oxycodone was cost-effective was 91% at \$5000 per patient improved.

Cost-utility Analysis

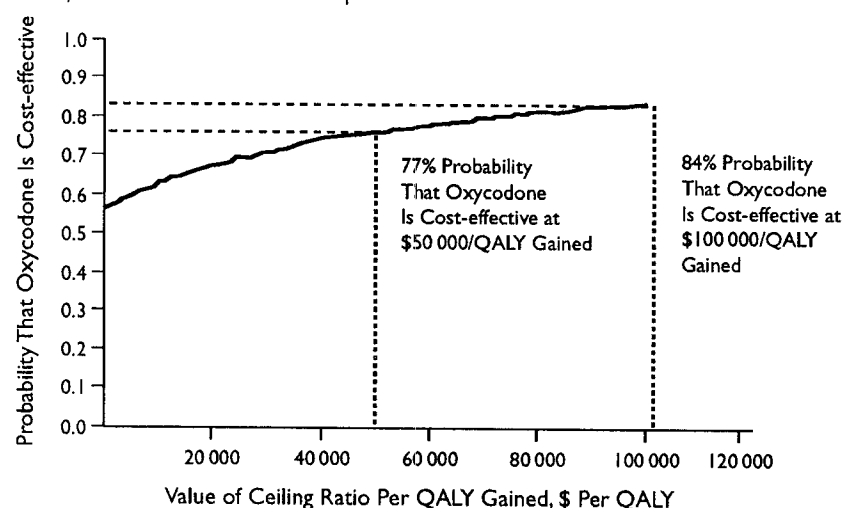
The findings of the CUA differ depending on the perspective. From the HCS perspective, the incremental cost per QALY gained for oxycodone compared with oxycodone-acetaminophen was \$75 810 per QALY gained. From the societal perspective, oxycodone was

Figure 1. Cost-effectiveness Acceptability Curve for the Cost-utility Analysis From the Healthcare System Perspective



QALY indicates quality-adjusted life-year.

Figure 2. Cost-effectiveness Acceptability Curve for the Cost-utility Analysis From the Social Perspective



QALY indicates quality-adjusted life-year.

more effective and less costly compared with oxycodone-acetaminophen. From the HCS perspective, the probability that oxycodone was cost-effective was 29% at \$50 000 per QALY gained and 60% at \$100 000 per QALY gained from the HCS (Figure 1). From the societal perspective, although treatment with oxycodone dominated treatment with oxycodone-acetaminophen, the probability that oxycodone was cost-effective was 77% at \$50 000 per QALY gained and 84% at \$100 000 per QALY gained (Figure 2).

Is a gain of 1 QALY for \$75 810 a good value? One approach to answer this question is to compare the results of other similar high-quality studies. Chapman et al³⁸ reviewed the literature for high-quality cost-utility studies that met the minimum methodological standards recommended by the US Public Health Service Panel on Cost-effectiveness in Health and Medicine.³⁹ Table 5 is a league table of such "panel-worthy" studies, with results adjusted to 2005 US dollars using the Consumer Price Index for medical care.²⁶ Because there was only 1 panel-worthy study in the musculoskeletal disease category, studies from other disease categories (eg, digestive system) were included.

From the HCS perspective, oxycodone had a higher cost-utility ratio compared with the other interventions listed in Table 5. However, from the societal perspective, oxycodone had the best cost-utility ratio in the table.

Another approach to address the question of value is to compare the results with an external standard. In the United States, a threshold of \$50 000 to \$100 000 per QALY gained is often referenced as a range for moderate evidence for adopting an intervention.^{41,42} From the HCS perspective, the cost-utility results in our study fall within this commonly accepted range in the United States. From the societal perspective, with increased QALYs gained and decreased incremental

costs, the results are clearly in favor of adoption of oxycodone treatment.

Study Strengths

This economic analysis of oxycodone was designed using the methodological guidelines for high-quality economic evaluations of pharmaceuticals developed by the Washington Panel on Cost-effectiveness.³⁹ Based on the guidelines, our study measured effectiveness in routine clinical practice and randomized patients to 2

Table 5. Cost per Quality-adjusted Life-year (QALY) Gained League Table

Reported Cost per QALY Gained, \$*	Adjusted Cost per QALY Gained, \$†	Treatment and Comparator
Healthcare system perspective		
Cost saving	Cost saving	Total hip arthroplasty vs no total hip arthroplasty in white women aged > 60 y with hip OA ³⁸
5500	7334	Total hip arthroplasty vs no total hip arthroplasty in white men aged ≥ 85 y with hip OA ³⁸
6500	8667	Appropriate care with hylan G-F 20 vs appropriate care without hylan G-F 20 for knee OA ³³
11 000	14 667	Prophylaxis for NSAID-associated gastric ulcers with low-dose misoprostol (100 µg 4 times daily) for persons aged > 60 y vs no prophylaxis for all among patients with rheumatoid arthritis taking NSAIDs ³⁸
12 000	16 000	Prophylaxis for NSAID-associated gastric ulcers with low-dose misoprostol (100 µg 4 times daily) for all vs prophylaxis for persons aged > 60 y among patients with rheumatoid arthritis taking NSAIDs ³⁸
75 810 (2005 US \$)	75 810 (2005 US \$)	Present study
Societal perspective		
Cost saving	Cost saving	Present study
6600	8800	Appropriate care with hylan G-F 20 vs appropriate care without hylan G-F 20 for knee OA ³³
205 000 (1997 US \$)	282 071	Aquatic exercise class ≥ 2 times/wk vs no exercise and usual care (< 1 h exercise/wk) in patients with OA aged 55-75 y ⁴⁰

*The reported cost per QALY gained data in most cases are the results reported by Torrance et al,³³ which were adjusted to 1998 US dollars.

†Adjusting to 2005 using the Consumer Price Index (CPI). Costs reported in 1998 US dollars were adjusted by the CPI factor of 322.8/242.1 to obtain a final cost for 2005. Costs reported in 1997 US dollars were adjusted by the CPI factor of 322.8/234.6 to obtain a final cost for 2005. As 2005 annual CPI was not yet available at the time of analysis, 2005 CPI adjustment was calculated as the average of reported CPI for January to November 2005. OA indicates osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug.

treatment arms (oxycodone and oxycodone-acetaminophen) to minimize bias. Oxycodone-acetaminophen was selected as the comparator because it contains the same active opioid component as oxycodone, is often prescribed on an as-needed basis for patients with moderate-to-severe OA, and has a leading market share among OA-related pain medications.

To improve the generalizability of the results to routine practice, the study was not blinded. Physicians had access to the full complement of routinely available therapies. Patients were enrolled from 50 centers that are representative of all US census regions. The large sample size allowed for robust estimates of costs and effectiveness.

This study captured prospectively a broad range of resources (hospitalizations and emergency department visits, diagnostic tests and procedures, assistive devices, etc), so that actual resources consumed were documented and not estimated. Costs associated with the trial protocol were not included, and protocol-driven costs were limited by using telephone interviews. Resource utilization also included time lost (an indirect measure of morbidity) from work and from unpaid activities from

the societal perspective. As specified by the guidelines, we conducted extensive sensitivity analyses to assess the robustness of the findings, including 1-way and probabilistic sensitivity analyses.

Study Limitations

One of the strengths of the study (the fact that it was open label so that treatment patterns would mimic real clinical practice) is also a limitation. Patients or physicians could have been biased in favor of 1 treatment. It was not possible to measure downstream costs and consequences in patients who discontinued the study, and extending the study duration longer than 4 months may have improved the data reliability by measuring costs and consequences during a longer period to establish stable outcomes and resource utilization patterns.

The study collected self-reported data via telephone interview (which was not verified with source medical charts). Therefore, patient responses could have been affected by recall bias. However, because the potential interview biases would have been similar in both groups, it is unlikely that the differential effect observed in this study is associated with the data source.

CONCLUSIONS

To our knowledge, this study is the first to evaluate the effect of oxycodone compared with oxycodone-acetaminophen in terms of health outcomes and resource utilization in a naturalistic setting in patients with moderate-to-severe OA of the hip or knee. Oxycodone was more effective compared with oxycodone-acetaminophen, as measured by the proportion of patients who improved and the QALYs gained. The use of oxycodone also fell within the acceptable range of cost-effectiveness if decision makers are willing to pay between \$50 000 and \$100 000 per QALY gained (from the HCS perspective). The sensitivity analysis showed that the probability that oxycodone use was cost-effective was 29% at the decision threshold of \$50 000 per QALY gained and 60% at \$100 000 per QALY gained.

Moreover, from the societal perspective, in which time lost from work and other normal activities is included in the calculation of costs, oxycodone was more effective and less costly than oxycodone-acetaminophen. The results are robust based on extensive sensitivity analyses. These findings should be considered in decisions about managing OA pain.

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